

WHAT IS CLAIMED IS:

1. A polypeptide derived from HCV polymerase NS5B having an HCV polymerase activity and consisting of an amino acid sequence X-Y, wherein X is a consecutive amino acid sequence which is a portion of the NS5B, an N-terminal amino acid of X is the amino acid residue 1 (Ser) of the NS5B, and a C-terminal amino acid residue of X is any one of amino acid residues 531 (Lys) to 570 (Arg) of the NS5B; and wherein Y is a carboxyl group or an amino acid sequence which is not derived from NS5B; and one or more amino acids in the amino acid sequence of X may be modified, and methionine residues in the amino acid sequence of X may be replaced by selenomethionine residues.
2. The polypeptide of claim 1, wherein the C-terminal amino acid residue of X is any one of amino acid residues 536 (Leu) to 552 (Val) of the NS5B.
3. The polypeptide of claim 2, wherein the C-terminal amino acid residue of X is any one of amino acid residues 536 (Leu) to 544 (Gln) of the NS5B.
4. The polypeptide of claim 2, wherein the C-terminal amino acid residue of X is any one of amino acid residues 531 (Lys) to 544 (Gln) in the NS5B.
5. The polypeptides of any one of claims 1 to 4, wherein methionine residues in the amino acid sequence of X are replaced by selenomethionine residues.
6. The polypeptides of any one of claims 1 to 5, wherein Y is an amino acid sequence not derived from NS5B, and said amino acid sequence is suitable for a column purification.
7. The polypeptides of any one of claims 1 to 6, wherein the NS5B comprises an amino acid sequence of SEQ ID NO: 1.
8. The polypeptide of claim 1, wherein said polypeptide is identified by an three-dimensional structural coordinates shown in Table 2 or 3.
9. A crystal comprising the polypeptide of any one of claims 1 to 8.
10. A DNA encoding the polypeptide of any one of claims 1 to 8.
11. A method for determining a three-dimensional structural coordinates of a cocomplex or a variant of HCV polymerase NS5B by the molecular replacement method using a three-dimensional structure coordinate of said NS5B.

12. A method for designing or identifying HCV polymerase inhibitors, which comprises determining the complementarity of a test compound with an active site and/or RNA binding cleft of a polypeptide using the three-dimensional structural coordinate of said polypeptide or its part and the three-dimensional structural coordinate of the test compound, wherein said polypeptide is derived from the HCV polymerase NS5B having an HCV polymerase activity and consisting of an amino acid sequence X-Y, wherein X is a consecutive amino acid sequence which is a portion of the NS5B, an N-terminal amino acid of X is the amino acid residue 1 (Ser) of the NS5B, a C-terminal amino acid residue of X is any one of amino acid residues 531 (Lys) to 570 (Arg) of the NS5B; and wherein Y is a carboxyl group or another amino acid sequence which is not derived from NS5B; and one or more amino acids in X may be modified, and methionine residues in the amino acid sequence of X may be replaced by selenomethionine residues.

13. A method for designing or identifying HCV polymerase inhibitors, which comprises the steps of:

(a) determining the complementarity of a test compound with an active site and/or RNA binding cleft of the a polypeptide using a three-dimensional structural coordinate of said polypeptide or its part and a three-dimensional structural coordinate of said test compound, wherein said polypeptide is derived from the HCV polymerase NS5B having an HCV polymerase activity and consisting of an amino acid sequence X-Y, wherein X is a consecutive amino acid sequence which is a portion of the NS5B, an N-terminal amino acid of X is the amino acid residue 1 (Ser) of the NS5B, a C-terminal amino acid residue of X is any one of amino acid residues 531 (Lys) to 570 (Arg) of the NS5B; and wherein Y is a carboxyl group of another amino acid sequence which is not derived from NS5B; and one or more amino acids in X may be modified, and methionine residues in the amino acid sequence of X may be replaced by selenomethionin residues;

(b) determining HCV polymerase-inhibitory activity of said test compound; and

(c) designing or determining HCV polymerase inhibitors using the complementarity data of said test compound determined in the above (a), and the inhibitory activity data obtained in the above (b).

14. The method of any one of claims 11 to 13, wherein the three-dimensional structural coordinate of the polypeptide is any one of the three-

dimensional structural coordinates shown in Table 2 or 3.

15. A method for identifying HCV polymerase inhibitors, which comprises the steps of:

- (a) obtaining a polypeptide, which is derived from the HCV polymerase NS5B has an HCV polymerase activity, and consisting of the amino acid sequence X'-Y, wherein X' is a consecutive amino acid sequence which is a portion of the NS5B, an N-terminal amino acid of X' is the amino acid residue 1 (Ser) of the NS5B, a C-terminal amino acid residue of X' is any one of amino acid residues 531 (Lys) to 544 (Gln) of the NS5B; and wherein Y is a carboxyl group or another amino acid sequence which is not derived from NS5B; and one or more amino acids in X' may be modified, and methionine residues in the amino acid sequence of X' may be replaced by selenomethionin residues;

- (b) determining the HCV polymerase activity of said polypeptide by reacting said polypeptide obtained in the above (a) with a template RNA and substrates in the presence of a test compound;

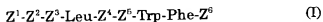
- (c) determining the HCV polymerase activity of said polypeptide by reacting polypeptide obtained in the above (a) with a template RNA and substrates in the absence of said test compound; and

- (d) comparing the HCV polymerase activity of the above (b) with the HCV polymerase activity of the above (c).

16. An HCV polymerase inhibitor, identified by the method in any one of claims 12 to 15.

17. An HCV polymerase inhibitor that inhibits the HCV polymerase activity of HCV polymerase NS5B by acting the boundary between the Thumb and Palm domains of NS5B.

18. The HCV polymerase inhibitor of claim 17, wherein said inhibitor is a polypeptide represented by the formula (I) or a pharmaceutically acceptable salt thereof:



- wherein Z¹ and Z⁶ each represent a hydrophilic group or an amino acid residue; Z² and Z³ each represent a single bond or an amino acid residue; and Z⁴ and Z⁵ each represent an amino acid residue.

ADD
E1